Remarks

Upon entry of the amendments, claims 1-11, 15, 25, 28-30, 39-47, 50-51, 77-79, 90, 97, 99, and 101-108 will be pending. Claims 52-59, 64-69, and 82-83 are canceled herein, without prejudice or disclaimer. Claims 12-14, 16-24, 26-27, 31-38, 48-49, and 80-81 were canceled in a previous amendment.

Claims 15, 51, and 77 have been amended to conform with the elections made in response to the Restriction Requirement. Claims 1, 46-47, 90 and 97 have been amended to more particularly describe the instant invention. Support for the amendment to claim 1 can be found in the specification as filed (*e.g.*, at least at page 37, lines 5-15). Support for the amendment to claim 90 can be found in the specification as filed (*e.g.*, at least at pages 44-45 (Example 7)). New claims 102-108 have been added herein. Support for these claims can be found throughout the specification and claims as filed. Accordingly, no new matter is presented in this amendment.

Restriction Requirement

The Examiner has deemed Applicants' traversal of the species election requirements non-persuasive. In an effort to facilitate prosecution of this application, Applicants have amended the claims to conform with the elected subject matter.

Specification

The Examiner objects to the specification for failing to comply with the sequence listing requirements. The specification has been amended to include the appropriate sequence identifier on page 12, line 14, and on page 32, line 24. A Substitute Sequence Listing and CRF are submitted concurrently herewith to reflect this change. Applicants submit that these documents place the specification in compliance with 37 CFR §§ 1.821-1.825. Thus, this objection should be withdrawn.

35 USC § 102

Claim 97 is rejected under 35 USC § 102(e) as anticipated by US Patent Application Publication No. US2003/0060438 ("Henry"). *See* Office Action at page 4. According to the

Examiner, Henry teaches a pharmaceutical composition comprising the amino acid sequence of SEQ ID NO:24. Applicants traverse as the reference is applied to the claims, as amended herein.

Claim 97 has been amended herein to recite an isolated peptide consisting of the amino acid sequence of SEQ ID NO:24, wherein the peptide is derived from a human neurokinin receptor, and wherein the peptide has the ability to penetrate biological barriers *in vivo*. Henry does not teach or suggest a pharmaceutical composition consisting of the amino acid sequence of SEQ ID NO:24. Moreover, Henry does not teach or suggest that a peptide containing amino acid residues 68-90 of the full length human neurokinin receptor protein (corresponding to SEQ ID NO:24 of the instant application) is able to penetrate biological barriers. Because Henry does not teach or suggest all the limitations of claim 97 as amended, Applicants contend that Henry cannot anticipate this claim. Thus, this rejection should be withdrawn.

35 USC § 112, ¶¶ 1 and 2

Claim 90 is rejected under 35 USC § 112, ¶ 1 for failing to comply with the enablement requirement. According to the Examiner, the specification fails to teach one of ordinary skill in the art how to make and use the kit of claim 90 without undue experimentation. *See* Office Action at pages 5-8. Claim 90 is further rejected as indefinite for failing to recite what the prophylactically or therapeutically effective amount of the composition in the kit is supposed to accomplish. *See* Office Action at page 9. Applicants traverse.

Claim 90 has been amended to recite a kit for treating diabetes comprising a therapeutically effective amount of the penetration composition of claim 15 (which indirectly depends from amended claim 1 and, therefore, includes a therapeutically effective amount of insulin, a counter ion to insulin, and a hydrophobized penetrating peptide) and a pharmaceutically acceptable carrier. Thus, Applicants assert that claim 90, as amended, particularly points out and distinctly claims the subject matter of the invention. Accordingly, Applicants submit that claim 90, as amended, meets the requirements of 35 USC § 112, ¶ 2. As such, this rejection should be withdrawn.

Applicants further contend that amended claim 90 is enabled such that one of ordinary skill in the art would know how to make and use the full scope of the claimed invention as of the filing date of the instant application, without undue experimentation. As previously discussed, claim 90 has been amended to recite a kit for treating diabetes comprising a therapeutically effective amount of a penetration composition comprising insulin, a suitable counter ion to insulin (*e.g.*, benzalkonium chloride), and a hydrophobized penetrating peptide (*e.g.*, SEQ ID NO:24). While the *Wands* factors are instructive in evaluating the enablement of a claimed invention, no one factor is dispositive in determining if the enablement requirement has been met, nor is it necessary to consider all the factors when determining enablement. *See Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 52 USPQ2d 1129, 1135-36 (Fed. Cir. 1999). Contrary to the Examiner's assertions, Applicants submit that the specification and working examples provide a high degree of guidance regarding how to make and use the components of the claimed kit. As a result, Applicants submit that the quantity of experimentation required to make and use the kit as claimed would not be undue.

For instance, Examples 1-3 and 6 teach the hydrophobization of SEQ ID NO:24 (via acylation, thereby providing SEQ ID NO:34) and the incorporation of the hydrophobized peptide into a penetration composition. Examples 5 and 7 show (albeit with different hydrophobized penetrating peptides) that the penetration compositions of the invention are effective in translocating insulin across a biological barrier and into the blood stream of mice, thereby reducing blood glucose levels. Thus, in view of these examples, and in view of the relative skill level of one skilled in the art (*i.e.*, an individual at the M.D. or Ph.D. level), Applicants submit that only routine experimentation would be required to hydrophobize SEQ ID NO:24 (rather than SEQ ID NO:26) in order to make and use a penetration composition according to the methods described in Examples 5 and 7.

Accordingly, in view of the various *Wands* factors such as the breadth of the claim as amended, the nature of the art, the relative level of skill in the prior art, the state of the prior art, the level of predictability in the art, the amount of guidance provided by the Applicants, the guidance provided by Examples 1-7 of the instant specification, and the quantity of experimentation necessary, Applicants assert that one of ordinary skill in the art would be able to make and use the invention of amended claim 90 as of the filing date of the instant application, without undue experimentation. Thus, this rejection should be withdrawn.

35 USC § 103(a)

Claims 1-11, 15, 25, 28-30, 39-47, 51, 77, and 90 are rejected under 35 USC § 103(a) for being obvious over US Patent Application Publication No. US 2004/0176476 ("Gyurik") in view of Henry. According to the Examiner, it would have been obvious to one of ordinary skill in the art at the time of invention to combine pharmaceutical compositions comprising insulin in the form of an emulsion mixed with benzalkonium chloride, membrane-compatible permeation enhancers, and aprotinin (as taught by Gyurik) with pharmaceutical compositions comprising the peptide provided by SEQ ID NO:24, bile salts, and penetration enhancers for increased delivery of the pharmaceutical composition (as taught by Henry). *See* Office Action at pages 10-12. The Examiner also rejects claims 77-79 as obvious over Gyurik in view of Henry and further in view of Ho et al., (2000) J. of Controlled Release, 68:433-440 ("Ho") and rejects claims 99 and 101 as obvious over Gyurik in view of Henry and further in view of US Patent No. 4,179,337 ("Davis"). *See* Office Action at pages 12-13. Applicants traverse these rejections as applied to the claims as amended and as they may apply to new claims 102-108.

As amended, independent claim 1, from which all remaining claims directly or indirectly depend, recites a penetration composition comprising a therapeutically effective amount of an effector, a counter ion to the effector, and a penetrating peptide, wherein the peptide has been hydrophobized.

Gyurik teaches a pharmaceutical composition useful for drug delivery across a body membrane. *See* Gyurik at ¶ 0001. The Gyurik composition can include, for example, a pharmaceutically active compound, such as insulin (*see* Gyurik at ¶ 0015), in an emulsion (*see* Gyurik at ¶ 0034), with a membrane-compatible permeation enhancer (*see* Gyurik at ¶¶ 0025-0033), benzylkonium chloride (*see* Gyurik at ¶ 0064), and aprotinin (*see* Gyurik at ¶ 0050). However, Gyurik does not teach or suggest any peptide having a translocating function as part of its pharmaceutical composition. More specifically, Gyurik does not teach or suggest the use of a human neurokinin-1 receptor, or any amino acid residues thereof (such as SEQ ID NO:24) that possesses a translocating function. Rather, Gyurik discloses the use of "Hsieh enhancers", which are cycloaliphatic enhancers that increases the rate of delivery of a pharmaceutically active compound through a biological membrane (*see* Gyurik at ¶ 0026).

The addition of Henry does not cure the deficiencies of Gyurik. The invention disclosed by Henry relates to the use of antisense oligonucleotides and non-nucleotide disruptor compounds to modulate the NK-1 receptor biosynthetic pathway to alleviate pain and inflammation. *See* Henry at ¶¶ 0001-0003. Henry does not teach or suggest that the NK-1 receptor peptide, or any portion thereof, has a translocation function useful for penetrating a biological barrier. While Henry refers to the use of penetration enhancers, that use of the penetration enhancers is meant to enhance the delivery of the NK-1 antisense oligonucleotide as the pharmaceutically-active agent, not to teach or suggest the use of a NK-1 receptor peptide modified with penetration enhancers as part of a penetration composition for the purpose of enhancing the delivery of another therapeutically-active agent.

Accordingly, Applicants submit that one of ordinary skill in the art at the time of invention would not have been motivated to combine the teachings of Gyurik and Henry to achieve the claimed invention. Moreover, even if the teachings of these references were combined, the combined teachings would not produce the penetration compositions as presently claimed. Specifically, one of skill in the art reading Gyurik would be led to modify the effector (*i.e.*, insulin) with a Hsieh enhancer, while simultaneously being led by Henry to modify a NK-1 receptor peptide with a second penetration enhancer. However, such a composition is not recited by the claims as amended. Rather, the combination of Gyurik and Henry teaches away from the claimed compositions.

For the above reasons, Applicants assert that the combination of Gyurik and Henry does not result in the claimed penetration compositions. Therefore, this combination of references is improper and cannot be used to establish a *prima facie* case of obviousness. Accordingly, the rejection of claim 1, as amended herein, should be withdrawn.

Similarly, claims 2-11, 15, 25, 28-30, 39-47, 51, 77, 90, and new claims 102-108, each depend (directly or indirectly) from amended claim 1 and necessarily incorporate all of the limitations of the claim. Thus, for the reasons discussed above, claims 2-11, 15, 25, 28-30, 39-47, 51, 77, 90, and new claims 102-108, are non-obvious in view of Gyurik and Henry. Accordingly, this rejection should be withdrawn.

Moreover, Applicants submit that claims 77-79, 99, and 101 are also non-obvious in view of the cited references. Ho teaches a multilayer design of pellets for nifedipine was

developed using pluronic F-68 to enhance the dissolution rate. *See* Ho, Abstract. Davis discloses a peptide that has been chemically modified in order to have polyethylene glycol residues attached to various amino acids of the peptide. *See* Davis, col. 2, lines 41-51. However, neither Ho nor Davis teaches or suggests a penetration composition comprising a therapeutically effective amount of an effector, a counter ion to the effector, and a penetrating peptide, wherein the peptide has been hydrophobized. Accordingly, the addition of Ho or Davis does not cure the deficiencies of the teachings of Gyurik and Henry.

Additionally, for the reasons previously discussed, the combination of references on which Ho and Davis are asserted is improper. Thus, Applicants submit that the rejection of claims 77-79, 99, and 101 as obvious in view of the combination of Gyurik/Henry and further in view of Ho or Davis, should also be withdrawn.

Conclusion

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. Should any questions or issues arise concerning this application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

With no extension of time, this response is due on or before February 23, 2006. The Commissioner is hereby authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 24348-501 CIP.

Respectfully submitted,

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